MANDELIC ACID B.D.H.

SODIUM MANDELATE B.D.H.

For use in the treatment of urinary infections
as a substitute for a ketogenic diet

THE BRITISH DRUG HOUSES LTD.
LONDON

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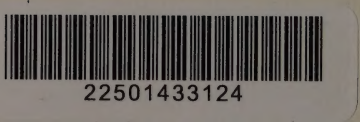

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Formula and properties of mandelic acid

Mandelic acid has the composition represented by the formula $C_6H_5CHOH.COOH$; it is a pure white crystalline hydroxy-acid which, after oral administration, is excreted unaltered in the urine which it renders bacteriostatic.

History of mandelic acid therapy

The medicinal use of mandelic acid as a urinary antiseptic is the outcome of an investigation (Rosenheim, M. L., *Lancet*, 1935, **I**, 1032) on the bacteriostatic effects of certain organic acids in relation to that of β-hydroxybutyric acid, which acid occurs in the urine of patients who have been kept on a ketogenic diet. Previously it had been reported (Fuller, A. T., *Lancet*, 1933, **I**, 855) that β-hydroxybutyric acid exercises in vitro a strong bacteriostatic action provided the reaction of the urine is below pH 5·3. The oral administration of β-hydroxybutyric acid for the treatment of urinary infections is ineffective by reason of the fact that this acid is oxidised completely on ingestion, but, as stated in the report of the investigation above mentioned, the possibility suggested itself that a keto- or hydroxy-acid might be found which would combine effective bacteriostatic power with resistance to oxidation in the body. Such an acid, if excreted unchanged in the urine and if non-toxic, might, on oral administration,

β-hydroxybutyric acid given orally ineffective

produce an effect similar to that produced by the ketogenic diet; thus this somewhat irksome form of treatment might be replaced by a more simple therapy.

Bacteriostatic power of mandelic acid

The result of the investigation demonstrated that the bacteriostatic power of mandelic acid compared favourably with that of β-hydroxybutyric acid, and that, in general, it fulfilled the desiderata of a satisfactory urinary antiseptic. When tested in vitro it was found that it possessed marked bacteriostatic powers against B. coli, and that urine passed three hours after the administration of mandelic acid would not support the growth of this organism at a low pH.

Necessity of maintenance of pH of urine at 5·3 or below

In mandelic acid therapy (as with the ketogenic diet) clinical improvement is possible only when the pH of the urine is maintained at a favourable point—5·3 or below. This is best effected by the oral administration of ammonium chloride, and the most suitable indicator for use in determining the pH of the urine has been found to be methyl red.

Mandelic acid administered as Sodium Mandelate B.D.H.

For therapeutic use, mandelic acid is always administered as the sodium salt. The sodium salt of Mandelic Acid B.D.H. is issued in the form of tablets (*vide* page 10); it is supplied also in bulk as the pure crystalline salt, Sodium Mandelate B.D.H. Pure crystalline Mandelic Acid B.D.H. (for neutralisation with sodium bicarbonate) is also available in bulk.

CLINICAL APPLICATION

Method of treatment of twelve cases

Further experimental work having demonstrated its non-toxicity, mandelic acid was subjected to clinical trial in twelve cases of urinary infection, six of which were cases of pyelitis of pregnancy; the routine method of treatment adopted was to give, in divided doses, 12 grammes daily of mandelic acid in the form of its sodium salt. The standard mixture used contained 3 grammes (45 grains) of

mandelic acid (neutralised with 1·6 grammes (24 grains) of sodium bicarbonate) in a fluid ounce of water suitably flavoured. A fluid ounce of this mixture was administered four times daily. The acidity of the urine was increased by giving eight 1 gramme (15 grains) cachets of ammonium chloride daily. The pH of the urine was taken regularly and was maintained below 5·3 by adjusting the ammonium chloride intake. The total liquid intake was limited to two pints daily.

In pyelitis of pregnancy and in chronic cystitis

Of the six cases of pyelitis of pregnancy, in two cases only did mandelic acid treatment fail to produce any effect (clinical or bacteriological), whilst it is stated in the report that complete recovery followed in the cases of chronic cystitis with B. coli infection treated with mandelic acid. Furthermore, it was found that, following the administration of mandelic acid, there was considerable improvement in the patients' general health: toxic effects disappeared rapidly and a marked diminution in such symptoms as headache, backache and frequency of micturition was observed. In chronic pyelitis, for example, persistent nocturnal frequency that had been resistant to other forms of treatment, including the ketogenic diet, ceased after only four days treatment with mandelic acid, a full night of unbroken sleep being enjoyed.

In general urinary infections

Of the six cases of general urinary infections unassociated with pregnancy that were treated with mandelic acid, all experienced clinical improvement, three of them being cured.

In resistant cases of pyelitis

In resistant cases of pyelitis intermittent therapy with mandelic acid is recommended on the assumption that the bacteria in the urine, not being eliminated rapidly, may tend to become resistant to the bacteriostatic agent.

Relapses in patients who, at some previous time, have suffered from urinary infections respond favourably to a short course of treatment with mandelic acid.

The conclusion drawn from the results of the twelve clinical cases reported upon was that '... *mandelic acid appears to be effective in cases of urinary infection unassociated with urinary obstruction*' (*Lancet*, 1935, **I**, 1032).

ADDITIONAL CLINICAL EVIDENCE

Successful treatment of hospital cases

The results of treatment with mandelic acid of a series of sixteen cases were reported in the *British Medical Journal* of December 7, 1935, p. 1096. The dosage in each instance was the usual one of 45 grains (3 grammes) four times daily. In these cases it was found that 6 capsules of 10 grains of ammonium chloride per day generally were sufficient to maintain the urinary pH below 5·5.

In two of the sixteen cases the urine became sterile in 5 days, and in two other cases in 6 days. Of the remainder, five cases became sterile in 8 days, three in 10 days and one in 12 days; in one case only was there failure to produce acid urine, and in one case treatment was stopped after 12 days owing to complications. The remaining case left the hospital after 8 days treatment, '*much improved*'.

In conclusion the authors stated that '. . . *Our results would seem to suggest that in mandelic acid a really efficient urinary antiseptic has been found, confirming the original claims made for the drug by Rosenheim. If this is so, this simple and practical treatment forms a really important therapeutic advance in the attack on a very common and disabling condition*'.

Cases treated in private practice

The following reports of cases treated with Mandelic Acid B.D.H., received since its administration has been adopted as a routine in many practices, are typical of many :—

CASE 1

Physician—suffered through B. coli infection for five years—was cleared of the infection after five weeks treatment with Mandelic Acid B.D.H.

CASE 2

Very bad B. coli infection—condition cleared up entirely (length of treatment not stated), and patient received extensive benefit.

CASE 3

Patient complained of violent pain in back and abdomen, appendicitis suspected but on exploration appendix was found to be normal. B. coli, Staphylococcus and Streptococcus were found in the urine. The condition cleared up entirely after ten days treatment with Mandelic Acid B.D.H.

CASE 4

Obstinate B. coli infection—cleared up in a month with Mandelic Acid B.D.H.

CASE 5

Cystitis, with an ascending nephritis infection—'*marvellous*' recovery through Mandelic Acid B.D.H., after months of ketogenic diet had failed.

MANDELIC ACID B.D.H. OUTFIT

Simplification of mandelic acid treatment

To facilitate the practice of mandelic acid therapy and to ensure the optimum response in the treatment of urinary infections, The British Drug Houses Ltd. have designed a special outfit containing the necessary quantity of Mandelic Acid B.D.H., in the form of tablets of Sodium Mandelate B.D.H., for a course of treatment lasting for fourteen days ; there are included also the accessories for controlling the pH of the urine.

Supplies for 14 days treatment

The Mandelic Acid B.D.H. Outfit consists of:—

56 tablets each containing 3·43 grammes of pure Sodium Mandelate B.D.H. equivalent to 3 grammes of Mandelic Acid B.D.H. The tablets are flavoured with lemon.

112 × 1 gramme capsules of ammonium chloride

A bottle of methyl red indicator

A test-tube marked to indicate 2 c.c.

A sealed tube containing a solution of methyl red buffered at pH 5.3 and forming a colour standard.

A dropping-pipette

The above items are supplied in a compact case.

Replacements available

Replacements for the outfit are available separately; tablets of Sodium Mandelate B.D.H. (flavoured with lemon) are packed in cartons of 8 tablets, whilst ammonium chloride capsules are supplied in lots of one dozen and over. Single bottles of methyl red indicator can be obtained if required.

DOSAGE AND TECHNIQUE OF TREATMENT

For adults

When the B.D.H. outfit is used four tablets of Sodium Mandelate B.D.H. should be given daily—one immediately after each meal. The tablet should be broken between the finger and thumb, dissolved in three or four tablespoonfuls of water contained in a tumbler and swallowed as a draught.

Precautionary measures against casts

According to the original recommendation the administration of each dose of mandelic acid should be followed by the administration of two capsules of ammonium chloride which should be swallowed with a little water; it is suggested, however, as a result of further investigations (*Lancet*, 1935, **2**, 741), which have been carried out since Mandelic Acid B.D.H. was first issued for clinical use, that there is a possibility of the occurrence of casts in highly acid urine; it is suggested further that the presence of such casts may be due rather to the action of the ammonium chloride than to that of the mandelic acid. It is recommended, therefore, that at the beginning of the treatment four capsules only

of ammonium chloride should be given daily, this dose being increased to six or eight capsules if it is found that the urine does not become sufficiently acid for the mandelic acid to exert its maximum bacteriostatic effect.

Duration of treatment

Clinical evidence demonstrates that most cases yield to treatment in ten to fourteen days or less. In particularly resistant cases or those in which there is a relapse, it is usual to submit the patient to a further course of treatment which may be started after an interval of ten days. During these intervals it is often advisable to prescribe large volumes of liquids to flush the urinary tract. It appears to be inadvisable to continue the treatment for more than fourteen days without a break.

For children

When Mandelic Acid B.D.H. is administered to children the dose must be carefully regulated; too large a dose may have a harmful effect upon the kidneys. In view of this it is advisable to start with small doses.

For children of 4 years of age or over, 2 grammes (30 grains), or about half a tablet, of Sodium Mandelate B.D.H. and 1 gramme (15 grains), the equivalent of one capsule, of ammonium chloride every 6 hours have been found suitable. For children of 1 to 4 years, the doses should be 1 gramme (15 grains), or about one-quarter of a tablet, of Sodium Mandelate B.D.H. and 10 grains, the equivalent of two-thirds of a capsule, of ammonium chloride, administered every 6 hours as with older children.

For infants

There appears to be no objection to mandelic acid treatment even in cases of infants under one year provided that the dosage is slightly smaller than that for children of 1 to 4 years. It has been found that ammonium chloride is best tolerated when it is administered in solution, flavoured with liquorice.

Mode of administration to the young

Great accuracy in measuring the dose of mandelic acid does not appear to be necessary, but to facilitate the administration of small doses to the young it will be found convenient to dissolve several doses at one time. Four tablets of Sodium

Mandelate B.D.H. dissolved in six ounces of water will produce a solution containing approximately 2 grammes (30 grains) of Sodium Mandelate B.D.H. in each ounce.

Similarly the ammonium chloride may be dispensed as a mixture with the liquorice. The following formula, or appropriate variations of it, will probably meet the requirements of most cases—

℞

Ammon. chlorid.		gr. x
Ext. glycyrrh. liq.		m. x
Aq. dest.	ad	℥i

M. ft. mist.

The small initial doses of the Sodium Mandelate B.D.H. mixture and of the ammonium chloride mixture may be increased after a few days if necessary, but this must depend upon the patient's general condition and the progress made towards urinary sterility.

METHOD OF DETERMINING THE ACIDITY OF THE URINE

As stated on page 6 clinical improvement with mandelic acid therapy is possible only by keeping the pH of the urine below 5·3 throughout the period of the treatment; therefore it is of the utmost importance that daily tests of the urine be made, and its pH controlled by the administration of ammonium chloride capsules.

The indicator, methyl red, used in determining the urinary acidity has a range of pH 6·3 to pH 4·2, that is, from weakly acid (yellow) to strongly acid (red). Between these two is a range of intermediate shades, one of which indicates pH 5·3.

A supply of methyl red is included in the Mandelic Acid B.D.H. Outfit; there is included also a sealed, colour-standard tube which contains a buffered methyl red solution at pH 5·3 for comparison with the shade of colour produced when the indicator is added to the urine.

The test should be carried out in the following manner :— By means of a small lipped enamelled jug transfer a sufficiency of the urine to be tested to reach the 2 c.c. mark on the test-tube supplied with the outfit. Draw a quantity of the methyl red indicator from the bottle into the dropping pipette supplied for the purpose, and add five drops of this indicator to the urine in the test-tube. Shake gently until the colour is uniform, then compare it with that of the liquid in the sealed, colour-standard tube supplied.

If the colour produced by the sample is more red than the standard, the urine is too acid ; the dose of ammonium chloride, therefore, should be reduced. On the other hand, if a yellowish pink colour is produced, it is an indication that the urine is insufficiently acid ; in this event the dose of ammonium chloride should be increased. The urine should also be examined regularly for the presence of albumin or casts (*vide* pages 10 and 14).

MANDELIC ACID THERAPY IN HOSPITAL PRACTICE

For use in hospitals and in those clinical practices in which facilities for determining the pH of the urine and other accessories for successful mandelic acid treatment of urinary infections are available (the B.D.H. outfit, therefore, being unnecessary), Mandelic Acid B.D.H. and Sodium Mandelate B.D.H. are supplied in pure crystalline form ; both the acid and the sodium salt are issued in standard packages from one ounce to seven pounds and in bulk.

Pure Sodium Mandelate B.D.H. is available for hospital use in tablets of 3·43 grammes, and supplies can be obtained in bulk quantities and in 500, 1000 and 5000 lots.

If the treatment be carried out with the acid itself 3 grammes of it may be neutralised with 1·6 grammes of sodium bicarbonate as recommended in the original paper (*vide* p. 7) ; on the other hand, if sodium mandelate be used 3·43 grammes are dissolved in 1–2 oz. of water, flavouring to taste being

added. Syrup of orange is neutral, but if syrup of lemon, which is acid, be used as a flavouring agent it should be neutralised with sodium bicarbonate. In other respects the treatment is carried out as described on pages 10 and 11.

CONTRA-INDICATION

Renal impairment the sole contra-indication

Inasmuch as mandelic acid is foreign to the body, and is not metabolised, renal irritation may occasionally be set up; hence, as a precautionary measure, repeated tests of the urine for the existence, or the increase, of albuminuria should be made. It is impossible in the presence of renal impairment for the kidneys to secrete a sufficiently acid urine to render the treatment effective; in consequence, since in such cases ammonium chloride may set up a general state of acidosis, mandelic acid therapy is contra-indicated in the presence of definite renal impairment.

As stated previously clinical evidence seems to indicate that there is a possibility that casts may occur in the urine of patients undergoing mandelic acid treatment, these being due to the action of ammonium chloride rather than to that of mandelic acid; the dose of ammonium chloride, therefore, should be kept as low as possible consistent with the maintenance of correct urinary acidity. The occurrence of casts, however, after full precautions have been taken is a warning that the whole treatment may have to be abandoned, particularly when mandelic acid therapy is being applied to children; indeed, for all child-patients, the initial dose of mandelic acid should be relatively small (*vide* p. 11). The only specific contra-indication for mandelic acid therapy, however, in children or adults is renal impairment.

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